(4)

No. 06-865

IN THE

Supreme Court of the United States

HERCULES INCORPORATED,
Petitioner,

v.

UNITED STATES OF AMERICA,
Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Eighth Circuit

BRIEF OF *AMICUS CURIAE* INDEPENDENT GROUP OF ESTEEMED SCIENTISTS JOHN DOULL, M.D., PHD., DAVID L. EATON, PH.D., HENRY C. PITOT, M.D., PH.D., GERALD N. WOGAN, PH.D., *ET. AL.* AND THE AMERICAN COUNCIL ON SCIENCE AND HEALTH

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INTERESTS OF *AMICI CURIAE* [1]

The *Amici* respectfully submit this brief in support of the Petitioner's request for a writ of certiorari. Specifically, the *Amici* support the Petitioner with regard to its request that this

[1] Pursuant to Rule 37.6, amici certify that no counsel for any party authored this brief in whole or in part. No persons other than the *amici curiae* or their counsel made a monetary contribution to the preparation or submission of this brief. Letters reflecting the parties' consent to the filing have been submitted to the Clerk.

Court entertain Question Number Two, "Whether the Environmental Protection Agency's use of its cancer potency factor for dioxin is contrary to the Administrative Procedure Act, 5 U.S.C. § 553. . .".

The *Amici* are world renowned leaders in the fields of toxicology, pharmacology, oncology, pathology, cancer molecular biology, carcinogenesis, cancer epidemiology, and cancer risk assessment. The *Amici* are interested in assuring that important science-based decisions be founded on accepted principles and biological concepts and that the weight of the scientific evidence be a determining factor in the decision-making process.

Gerald N. Wogan, Ph.D. is Emeritus Professor of Toxicology and Chemistry at the Massachusetts Institute of Technology (MIT). He was Director of the Division of Toxicology and Head of the Department of Applied Biological Sciences. He is a Member of the National Academy of Sciences and the Institute of Medicine. He has served on the National Institutes of Environmental Health Sciences (NIEHS) Advisory Council, the National Cancer Institute (NCI) Advisory Board, and the Science Advisory Board of the U.S. Environmental Protection Agency (EPA). Dr. Wogan was recently awarded the General Motors Research Cancer Foundation Mott Prize for his lifetime contributions to cancer cause and prevention.

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The American Council on Science and Health is a consumer education consortium whose members include hundreds of scientists and health professionals.

SUMMARY OF THE REASONS FOR GRANTING THE WRIT

The *Amici* believe that the Writ for Certiorari presents an important legal issue with regard to whether the Environmental Protection Agency can ignore the overwhelming scientific consensus in rendering pervasive regulatory decisions and whether it can avoid accountability and review of its actions. In arriving at the critical decision in its dioxin cancer management program, the cancer potency factor, the EPA disregarded well established principles of pharmacology

and molecular biology in adopting a linear, rather than a threshold-based risk model. The fact that the EPA has ignored the scientific consensus is clearly established by a recent report of the National Academy of Sciences/National Research Council. Moreover, the EPA has failed on numerous occasions to provide adequate scientific bases for rejecting this scientific consensus in favor of a threshold model. These failures dictate a need for this Court to determine whether EPA should be required to hold an APA hearing with all the procedural due process provided therein.

REASONS FOR GRANTING THE WRIT

As scientists interested in cancer risk management, we support the Petitioner's Request for a writ of certiorari. Specifically, we ask this Court to grant the Writ on the issue as to whether the Environmental Protection Agency should be required to hold a hearing, pursuant to the Administrative Procedure Act, 5 U.S.C. § 553 (APA), on the dioxin cancer potency factor. This potency factor is key to formulating a science-based cancer risk management program.

We believe the writ poses an issue of exceptional importance. It presents the question whether the weight of the scientific evidence, as opposed to rigid adoption of a default principle or a particular philosophy, will be the basis for critical regulatory decisions that have a significant effect on us all.

The *Amici* believe that science should be in the forefront in these types of important regulatory and societal decisions. The *Amici* suggest to this Court that when there is a clear worldwide scientific consensus, as there is in this case, the consensus should be a key element in the decision-making process. In this instance, there has been no formal hearing. The worldwide scientific consensus has been ignored in favor of a default decision which even the EPA admits lacks a strong scientific foundation.

The *Amici* are concerned about the scientific, economic, and social consequences of a regulatory process that ignores the well-established scientific principles and avoids accountability and review of its actions.

The *Amici* have taken the extraordinary step of filing this brief in support of the Petitioner's request because we believe that the overwhelming scientific evidence is contrary to the EPA's adoption of a linear approach to modeling cancer risk when the chemical in question (in this case dioxin) is a promoter and causes cancer through a non-genotoxic receptor-mediated mechanism. For these kinds of chemicals, there exists a strong presumption that a threshold-based risk assessment is warranted. Absent overwhelming supporting evidence, the use of a purely linear- based model to calculate cancer risk, as EPA has done in this case, is scientifically indefensible.

Consistent with this presumption, The Joint FAO/WHO Expert Committee on Food Additives in its 2002 evaluation of dioxin's toxicity concluded "that a tolerable intake could be established for TCDD on the basis of the assumption that there is a threshold for all effects, including cancer". World Health Organization, *Evaluation of Certain Food Additives and Contaminants* (2002) pg. 141.

The consequences of the misuse of a linear-based model are significant. For example, the EPA in 1993, using the linear model, set the acceptable daily intake of dioxin at 6 fg/kg/day. The Canadian Health and Welfare Department, using a threshold model, set acceptable daily intakes at 10, 000 fg/kg/day.

Amici do not ask this Court to evaluate the scientific merits. Nor do we ask this Court to weigh competing scientific principles. What we do ask is that this important scientific debate be the subject of a formal hearing under the APA, the decision be based on the weight of the scientific

evidence, and that the ruling be subject to the scrutiny provided by judicial review.

In December 2003, the EPA released a preliminary draft document titled *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds,* referred to as the Reassessment. In its risk characterization of dioxin, the EPA made several statements with which we agree:

> It is important that this characterization convey the current understanding of the scientific community regarding these issues, highlight uncertainties in this understanding, and specify where assumptions have been used or inferences made in the absence of data.
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> . . .
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> Binding of dioxin-like compounds to a cellular protein called the aryl-hydrocarbon receptor (AhR) represents the first step in a series of events attributable to exposure to dioxin-like compounds, including biochemical, cellular, and tissue-level changes in normal biological processes. Binding to the AhR appears to be necessary for all well-studied effects of dioxin, but it is not sufficient in and of itself to elicit these responses.
>
> . . .
>
> There is general agreement that the mode of TCDD's carcinogenicity is as an AhR dependent promoter and proceeds through gene expression and/or a modification of the action of a number of receptor and hormone systems involved in cell growth and differentiation, such as the epidermal growth factor receptor and the estrogen receptor.

pgs. 6-1, 6-4, 6-8

The *Amici* would like to provide the scientific information that would permit this Court to understand the significance of these statements. It should be noted that this science is not

novel. The fundamental scientific principles and data have existed for more than twenty years.

First, let us address the question of what is a cancer potency factor.

Nearly all relevant cancer risk data from human epidemiologic studies and experimental animal bioassays reflect doses much higher than those typically experienced by humans from exposure to dioxin. In order to manage cancer risk at levels normally experienced by humans, there must be an extrapolation from the existing data to low level exposures. This extrapolation involves two critical decisions: (1) selecting a "point of departure" (POD), which corresponds to the lowest dose associated with observable adverse effects within the range of data, and (2) selecting the mathematical model used to extrapolate risk for typical human exposures that are well below the POD. These calculations lead to the cancer potency factor, which in turn dictates the important cancer risk management decisions.

Estimating risks below the POD requires making assumptions about how dioxin might cause cancer at the lower exposures. A linear mathematical model assumes that there is a proportional cancer risk at all levels of exposure above zero, regardless of how small the exposure. A threshold model projects that there is a level below which the exposure does not present a cancer risk.

Next, let us explore the significance of the fact that the mode of dioxin's carcinogenicity is receptor-mediated, that is, dependent on the Ah receptor. First, we need to understand what is cancer.

Cancer is a group of more than one hundred diseases in which abnormal cells grow and spread unrestrained throughout the body. The dominant characteristic of cancer is uncontrolled cell growth resulting from loss of control over cell proliferation and cell survival. Cancer cells proliferate

excessively. They are no longer subject to most of the normal controls on cell growth.

Normal cells have multiple mechanisms to regulate their growth. They reproduce only when instructed to do so. Also, they undergo programmed cell death which occurs in an absolutely predictable pattern. Cancer cells, in stark contrast, violate this scheme. They become deaf to the usual controls on growth and follow their own internal agenda for reproduction. Cells replicate when they are supposed to be non-producing. Cells live when they are programmed to die.

What do receptors have to do with cancer? Normal cellular function is dependent on the cell's ability to process signals that the cell receives from sources outside and inside the cell. Cells need to sense the appropriate time to grow, divide, migrate, differentiate, survive or die. Cells contain an elaborate system of proteins that enable the cell to respond to these signals. These proteins are called receptors. AhR is such a receptor. Once activated, these receptors initiate signalling pathways which determine the response of the cells. Aberrant activation of one or more of these pathways can lead to unregulated cell division and the formation of a tumor.

The sequence of events associated with the AhR receptor-mediated mechanism can be explained as involving (a) entry of the dioxin into the cells, (b) binding of dioxin to the Ah receptor, (c) binding of the receptor-dioxin complex to DNA recognition sites, and (d) overexpression of specific genes relating to cell proliferation and cell death.

Signals from outside the cell (including exogenous chemicals such as dioxin) are recognized by the receptors on or within the target cell. The signalling molecule, which is referred to as a ligand, binds to the receptor. Binding of a ligand to a receptor may convert the receptor from an inactive to an active form which then initiates a chemical response in

the target cell. Activation of a receptor, such as the Ah receptor by dioxin, in and of itself is not sufficient to produce a biological effect.

After a complex series of processes, the activated receptor may bind to a certain region of the DNA. The DNA is the permanent repository for the genetic information of the cell. The function of the DNA is to direct the activities of the cell, including cell proliferation and programmed cell death. The DNA directs these activities through the manufacture (synthesis) of a huge variety of proteins which determine the behavior of the cell. This is known as gene expression.

Under the right circumstances, the activated dioxin-AhR receptor complex can bind to specific regions of the DNA known as dioxin responsive elements, or DREs. Those responsive elements of the DNA can affect cell proliferation and cell survival. This binding can alter gene expression, resulting in abnormal cell growth and survival of cells that normally would be programmed to die.

This upregulation of gene expression in itself does not cause cancer. It can, however, "promote" an existing cancer-prone cell.

This receptor-mediated mechanism implies a series of thresholds. First, there must be a sufficient quantity of ligand to result in receptor activation. Second, the biological response of the receptor to the ligand is non linear. Third, a sufficient number of receptors must be activated in order to send a potent enough signal to affect gene expression and ultimately cell proliferation and cell survival. There are other thresholds involved in receptor-mediation.

As we stated earlier, EPA accepts the fact that dioxin's carcinogenicity is receptor-mediated and proceeds through gene expression and/or a modification of the action of a number of receptor and hormone systems involved in cell growth and differentiation, such as the estrogen receptor.

Consequently, the science dictates that, at the very least, there is a strong presumption that dioxin's carcinogenicity is subject to a threshold and that threshold concepts should be utilized in modeling its cancer risk. These principles have been confirmed through extensive study of the estrogen receptor referenced by EPA.

There is general acceptance that dioxin operates as a promoter. EPA has classified dioxin as a strong promoter in its 2003 Reassessment of TCDD. What does that designation tell us as to whether dioxin should be managed on the basis of a threshold or linear model?

There are two broad classes of chemical carcinogens: genotoxic chemicals and non-genotoxic chemicals. Genotoxic chemicals directly damage the DNA and thereby mutate the genetic code. These chemicals are classified as initiators.

Non-genotoxic chemicals do not damage the DNA and thereby do not cause mutations in the genetic code. Non-genotoxic chemicals interfere with gene expression and growth factor signalling, thereby affecting normal cell regulation and resulting in proliferation of unwanted cells or the presence of "anarchic" cells that should be eliminated. There is no dispute that dioxin is a non-genotoxic chemical.

Nor is there any dispute that dioxin is a promoter. Promoters do not begin the cancer process. Mutations to the DNA are at the heart of cancer induction. Promoters do not cause mutations to the DNA. Rather, they enhance the development of cancer by expanding the population of cells that carry mutations.

Cells with mutations grow at a faster rate than normal cells, resulting in the clonal expansion of the cells carrying the mutation. The more cells there are carrying the growth enhancing mutation and the more times they divide, the greater the chance they will go through other mutations, carrying those cells one more step along the road to becoming cancer cells.

It has been well accepted for more than twenty years that promoters of carcinogenesis are non linear and exhibit thresholds of biological response. Consequently, the recognition that dioxin is a strong promoter implies a significant threshold aspect to its carcinogenicity.

Fortunately, this Court has the benefit of a recent critique by the National Academy of Sciences/National Research Council of EPA's 2003 Reassessment of TCDD. This critique was conducted by a committee of eighteen of our country's leading experts in cancer risk assessment. The committee was chaired by David L. Eaton, who is a party to this Amicus Brief.

In 2004, EPA requested the NRC to create an expert committee to review its 2003 Reassessment. In response, the NRC appointed the above Committee. The Committee was charged to review, among other things, EPA's modeling assumptions. The charge specifically requested that the Committee address the validity of the nonthreshold linear dose response model utilized by EPA in formulating its dioxin cancer potency factor.

After reviewing volumes of data, the Committee summarized its conclusions with regard to estimating dioxin's cancer risk as follows:

> Because nearly all data (both human epidemiologic studies and experimental animal bioassays) relevant to cancer risk are for doses much higher than those to which the general human population is typically exposed, analysts must extrapolate below the doses observed when estimating risks. This extrapolation depends on first fitting a dose response curve to the observed data from a given study and choosing a "point-of-departure" (POD), which corresponds to the lowest dose associated with adverse effects within the range of the data from the experiment or study.
>
> . . .

> This extrapolation must be based on assumption about how TCDD . . . might cause cancer. Thus, the selection of the type of mathematical model used to extrapolate below the POD is a critical decision in the cancer risk assessment process. In the 2003 Reassessment, EPA chose to extrapolate below the POD with a "linear" model which assumes that the biological response increases proportionally with the level of exposure starting at a dose of zero. Risk assessments based on this approach are general higher than those based on alternative "non linear" assumptions, where the biological response does not vary proportionately with the dose.
>
> . . .
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> After reviewing EPA's 2003 Reassessment and additional scientific data published since completion of the Reassessment, *the committee unanimously agreed that the current weight of scientific evidence of the carcinogenicity of dioxin is adequate to justify the use of non linear methods consistent with a receptor mediated response to extrapolate below the POD.* [emphasis added] The committee points out the data from NTP [National Toxicology Program] released after EPA generated the 2003 Reassessment provide the most extensive information collected to date on TCDD carcinogenicity in test animals, and the committee found the NTP results to be compelling. The committee concludes that EPA should reevaluate dose-response relationships for TCDD. . . . *Specifically, the committee determines that the scientific evidence is consistent with receptor mediated responses and favor the use of a non linear model over the default linear assumption to extrapolate below the POD for dioxin-related cancer risk.* [emphasis added]

National Academy of Sciences, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (2006) pgs. 15-16.

The Committee offered several reasons for its conclusion that a non linear threshold approach is appropriate for dioxin cancer risk management. First, the Committee found that there is insufficient evidence that dioxin has initiating activity. They further found that dioxin enhanced tumor development through tumor promotion and that the promoting activity is mediated through the activation of the Ah receptor. This in turn leads to a variety of changes to gene expression, including those relating to cell proliferation. The Committee went on to state, "*There is general consensus in the scientific community that non genotoxic carcinogens that act as tumor promoters exhibit non linear dose response relationships, and that thresholds (doses below which the expected response would be zero) are likely to be present.*" [emphasis added]. *Id* at pg. 122.

Second, the Committee stated that a fundamental concept in pharmacology is that receptor-mediated responses have non linear dose relationships. "Response is a function of the number of occupied and activated receptors which typically exhibit steep dose response relationships." *Id* at pg.124.

Third, in its own 2005 cancer guidelines, EPA provides the following guidance on choosing between linear and non linear extrapolation approaches: "a nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses". *Id* at pg. 125.

Fourth, the recent NTP (National Toxicology Program) dioxin bioassay data provide evidence of non linearity.

In summation, both the biology and the extensive review by the NRC Committee, in the opinion of the *Amici*, strongly support the writ for certiorari and the requested relief—requiring the EPA to hold an APA hearing and to base its dioxin cancer risk management on accepted scientific

principles and data. The EPA itself has acknowledged in its 2003 Reassessment that it is important its dioxin cancer risk management be consistent with the current understanding of the scientific community. Unfortunately, EPA has failed to act in a manner consistent with this important pronouncement.

The NRC Committee also commented that the EPA should more thoroughly justify and communicate its bases for its approach to dose-response modeling. Specifically, they stated "the selection of the default linear extrapolation approach was one of the most critical decisions in the Reassessment, but the decision to use this approach was not supported by a scientifically rigorous argument. . .". *Id* at pg. 196.

This criticism is not new. For example, in 1995 EPA's Science Advisory Board published a report criticizing EPA's failure to articulate and explain its reasons for its dioxin linear modeling approach. Moreover, the EPA in the 1990's was repeatedly faulted for ignoring the scientific field of receptor technology. Among these critics was *Amici* Dr. Alan Poland who discovered the binding affinity relationship of dioxin to the Ah receptor. It should be noted that EPA has not altered its dioxin cancer potency factor since 1980 in spite of the many scientific advancements illuminating dioxin's modes of carcinogenicity.

The *Amici* believe that this continuing deficiency is another reason for this Court to grant the writ of certiorari.

CONCLUSION

The petition for writ of certiorari should be granted.

Respectfully submitted,

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